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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Supplemental Office Action Summary	Application No. 09/940,235	Applicant(s) SAHNI ET AL.	
	Examiner Sheridan L. Swope	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Interview summary in action*.

DETAILED ACTION

This Office Action replaces the action mailed February 10, 2006.

It is acknowledged that Applicant's response of November 23, 2005 cancelled all previously pending claims and added Claims 34-54. Claims 34-54 are hereby reexamined.

Specification-Objections

Amendment of the specification on page 8, paragraph 2, to include the references Young et al, 1995 and Jackson et al, 1986, is acknowledged. However, said amendment is improper, as it introduces New Matter. The original specification does not disclose said references.

The specification is objected because the table on page 57 should be amended to provide a table number and correct the formatting of the data.

The specification is objected to for failing to identify the sequences disclosed in the specification by sequence identifier numbers (SEQ ID NO:). 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. The sequence listing discloses 24 sequences. The specification fails to identify any of the sequence disclosed therein by any of said sequence identifier numbers (SEQ ID NO:). Correction is required.

The specification is objected to for referring to a figure, without indicating which figure. Page 55, lines 15 and 17, comprise the term "Fig. ", without a number. Correction is required.

Abstract

The abstract of the disclosure is objected to because the first phrase is not a complete sentence.

Drawings

Figures 3, 6, 11, 14, 17, 19, 21, and 22 are objected to for not providing sequence identifier numbers (SEQ ID NO:) for the sequences disclosed in said figures. Correction of said drawings, or the legends thereto, is required.

Figure 3 is objected to for improper labeling. The two panels of Figure 3 are labeled "FIG. 3-1" and "FIG. 3-2". Said labeling is inconsistent with standard formatting; wherein said panels should be labeled "FIG. 3A" and "FIG. 3B". Correction is requested.

Figure 6 and its legend are objected to for the following reasons. The legend to Figure 6 asserts that the figure discloses the polynucleotides encoding each of five fibrin binding domains, FBD(1-5)-encoding DNAs, "obtained from EMBL; the file and accession no.'s are ID-HSFIBI and X02761, K00799, K02273, X00307, X00739". However, Figure 6 discloses only a single sequence. Furthermore, the polynucleotide disclosed by EMBL accession number ID-HSFIBI is annotated as a DNA sequence surrounding human nuclear factor I binding site, not a fibrin binding domain. Clarification is required.

Figure Legends

The figure legends are objected to for the following reasons.

Fig 4: The identity of the streptokinase polynucleotide, from which the restriction map of Fig 4 is derived, should be stated.

Fig 7: The identity of the streptokinase polynucleotide, from which the restriction map of Fig 7 is derived, should be stated.

Fig 18: The figure legend is objected to for having a single hard bracket –]– at the end.

Appropriate corrections are required.

Information Disclosure Statement

If Applicants wish for the 22 references cited in their response of November 23, 2005, pages 23-26, to be printed on an issued patent, they should cite said references in an Information Disclosure Statement check that the references have been submitted.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For Claims 47 and 49, the phrase "a fibrin-binding component" renders the claims in definite. Claims 47 and 49 are dependent from Claim 34, which defines the fibrin-binding domains comprised by the polypeptide of Claim 34. It is unclear whether Claims 47 and 49 should read "the fibrin-binding component", referring to the fibrin-binding components defined in Claim 34 or whether Claims 47 and 49 are meant to mean "any fibrin-binding component". Claims 48 and 50-52, as dependent from Claims 47 and 49, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons. Clarification is required. For purposes of examination, it is assumed that Claims 47 and 49 are meant to refer to any fibrin-binding component.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement because, while the specification is enabling for the chimeric polypeptide encoded by the nucleic acid molecules set forth in Figs 17b, 19b, 21b, and 22b, the specification does not reasonably provide enablement for any chimeric polypeptide comprising a streptokinase component, wherein said chimeric polypeptide additionally comprises any linker region, wherein the linker region is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claim 34 is so broad as to encompass any chimeric polypeptide comprising a streptokinase component, wherein said chimeric polypeptide additionally comprises any linker region, wherein the linker region is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. Claims 35-54 provide addition limitations to the scope of chimeric polypeptides encompassed by Claim 34. However, all of said claims encompass chimeric polypeptides comprising a linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of chimeric polypeptides, as broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired functions for the linker region requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the chimeric polypeptides as set forth in Figs 17b, 19b, 21b, and 22b, which are disclosed by the specification as having a lag in clot lysis (pg 58, parg 2).

While recombinant and mutagenesis techniques and plasminogen activation assays are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino

acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 34-54 which encompass any chimeric polypeptide comprising a streptokinase component and any linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The specification does not support the broad scope of Claims 34-54 because the specification does not establish: (A) the structure of any linker polypeptide having the desired utility; (B) regions of any linker's structure which may be modified in order to support the desired activity to (i) prevent activation of plasminogen by said streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component; (C) regions of any linker's structure which may be modified without effecting the ability to (i) prevent activation of plasminogen by said streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component; (D) the general tolerance of the linker function to alterations in the structure of any linker peptide and extent of such tolerance; (E) a rational and predictable scheme for choosing any linker component, or modifying any residues thereof, of with an expectation of obtaining the desired biological function; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices of chimeric proteins is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of chimeric proteins comprising a streptokinase component and any linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In anticipation of the instant rejection, Applicants provided the following arguments.

Applicants' initial remarks summarize the legal basis for rejection under 35 U.S.C. 112, first paragraph.

(A) Capon v Eshhar v Dudas, 418 F.3d 1349 (Fed. Cir. 2005) has clarified that 35 USC 112 does not require re-analysis in the specification of that which was already known. The Board's rule that the nucleotide sequences of chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, ***is an inappropriate generalization***. (Applicants' emphasis)

(B) ***It is not necessary that every permutation within a generally operable invention be effective*** in order for an inventor to obtain a generic claim. (Applicants' emphasis)

(C) The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. An extended period of experimentation may not be undue if the skilled artisan is given sufficient guidance. If the skilled artisan can readily anticipate the effect of a change within the subject matter, there is predictability in the art. (MPEP 2164)

(D) Flexibility of the adjoining region [linker] is a key factor for predicting the plasmin-dependent activation kinetics of the disclosed constructs. SK-FBD4,5 and SK-FBD1,2, comprising GGGQAQQIV and GGGQAQQMV linkers, respectively, had a 10 min and 10.5 min lag, respectively. Using the flexible region naturally existing at the N-terminus of streptokinase, IAGPQWLL, gave an 8 min lag. Use of the linkers IAGPQWLL and GGGQAQQIV within the construct FBD4,5-SK-FBD4,5, provided an 18 min lag. Thus, the flexible regions can be used to predictably control the kinetics of plasmin-dependent activation of streptokinase. The Examiner is reminded that the flexibility of a peptide can be predicted from amino acid composition and is not dependent on specific primary sequence.

(A) Reply: It is acknowledged that well known teachings in the art need not be re-analyzed in the specification. It is also acknowledged that the prior art enables the skilled artisan to make a chimeric fusion protein comprising human fibronectin-derived fibrin binding domains (FBD) 1 and 2 or 4 and 5 and a streptokinase component (see the rejection of Claims 34-37, 41, and 42 under 103(a) below). However, the prior art fails to enable the skilled artisan to make and use any chimeric protein comprising a linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. Thus, the specification must enable the

skilled artisan to make and use such chimeric proteins. It is acknowledged that Example 3 teaches the making of a chimeric protein comprising the linker region, Gly-Gly-Gly, between an N-terminal streptokinase component and a C-terminal FBD4,5 component (SK-G_3-FBD4,5), while Example 4 teaches the making of a chimeric protein comprising the same linker region, Gly-Gly-Gly, between an N-terminal streptokinase component and a C-terminal FBD1,2 component (SK-G_3-FBD1,2). Examples 5 and 6 teaches the making of chimeric proteins comprising an N-terminal FBD4,5 component and a C-terminal streptokinase component (FBD4,5- SK) and an N-terminal and C-terminal FBD4,5 component with a central streptokinase component (FBD4,5- SK- FBD4,5), respectively. It is noted that neither of Examples 5 and 6 teach that said chimeric proteins comprise a linker. It is also acknowledged that the specification teaches that activation of plasminogen by said constructs shows a lag of 10-12 mins for SK-G_3-FBD4,5 or SK-G_3-FBD1,2, a lag of 7-8 mins for FBD4,5-G_3- SK, and a lag of 20-25 mins for FBD4,5-SK-FBD4,5, compared to no lag for native streptokinase (pg 55, parg 1). Based on said teachings a person of ordinary skill in the art would believe that, more likely than not, the lag time seen with the chimeric proteins vs the native streptokinase is not due to the presence or absence of a linker, but to the presence or absence of fibrin binding domains. Likewise, the skilled artisan would believe that the effect of plasmin on the lag period (pg 55, parg 2 – pg 56, parg 1) is, more likely than not, due to the presence or absence of fibrin binding domains, not the presence or absence of a linker. Thus, the specification has failed to enable the skilled artisan to make and use a chimeric protein comprising a linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-

dependent activation of the streptokinase component because the linker appears to be irrelevant to said activation processes.

(B) Reply: The instant rejection is not based on the premise that every permutation within the recited invention be effective; but, is based on the fact that neither the specification nor the art enable the skilled artisan to make and use the full scope of the recited invention without undue experimentation. As explained in (A) above, (D) below, and the prior action, the specification fails to enable the skilled artisan to make and use any chimeric protein comprising a streptokinase component and any linker peptide that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component.

(C) Reply: As explained in (A) and (B), above, undue experimentation would be necessary to practice the recited invention. Neither the art nor the specification teach any linker having the required functional properties, or provide guidance on how to make and use such a linker. Undue experimentation would be required to make and test an essentially unlimited number of linkers for the properties of being sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. While recombinant and mutagenesis techniques and plasminogen activation assays are known, it is not routine in the art to screen an essentially unlimited number of chimeric proteins for the desired activity, as encompassed by the instant claims.

(D) Reply: The specification fails to distinctly assert that the specific peptides GGGQAQQIV, GGGQAQQMV, and IAGPQWLL function as flexible linkers in the recited chimeric proteins or to distinctly assert that said peptides (i) prevent activation of plasminogen

by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. The specification also fails to provide evidence that (i) said linkers have differences in flexibility or (ii) that differences in flexibility are responsible for differences in the lag time for plasminogen activation. Hindsight reasoning cannot be used to provide evidence for enablement that is lacking in the specification as filed. Furthermore, as described above, the differences in lag times for plasminogen activation could be due to differences in the type, number, and/or position of the fibrin-binding domains. Moreover, Jackson et al, 1986 teach that a fragment of streptokinase consisting of residues 1-383 streptokinase exhibits a lag in activation of plasminogen (Fig 4), suggesting that a "flexible linker" is not necessary for regulating the initial rate of plasminogen activation.

For these reasons, Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

Written Description

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claims 34 and 47 introduce the limitation of "a region that is sufficiently flexible so as to prevent activation of plasminogen by said streptokinase component". The specification fails to describe said limitation and, thus, Claims 34 and 47, as well as dependent Claims 35-46 and 48-54, are rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of chimeric proteins comprising a streptokinase component capable of plasminogen activation and a linker peptide, wherein the linker peptide is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. The specification teaches the structure of no representative species of such chimeric proteins. Moreover, the specification fails to describe any representative species by any identifying characteristics or properties other than the functionality being a chimeric protein that can, due to the flexibility of the linker, activate plasminogen only after a lag. Given this lack of description of the structure of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants' arguments that are relevant to the instant rejection, and the Examiner's responses, are presented above under the enablement rejection.

Claims 37-40 and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claims 37 and 49 introduce the limitation of "the flexible region ...comprises the N-

terminal region of SEQ ID NO: 2". The specification fails to describe said limitation and, thus, Claims 37 and 49, as well as dependent Claims 38-40 and 50-52, are rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Prior rejection of Claims 3, 32, and 33 under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994 and further in view of Goldstein et al, 1996 is rendered moot, as said claims have been cancelled.

Claims 34-37, 41, and 42 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and further in view of Dawson et al, 1995. Malke et al teach a fusion protein comprising streptokinase and the fibrin binding domains from plasminogen (Example 1). Goldstein et al teach a fusion protein comprising streptokinase and an anti-fibrin antibody (Fig 6), wherein the streptokinase exhibits a lag in activation (Fig 4). Both of the fusion proteins of Malke et al and Goldstein et al target streptokinase to a fibrin clot.

Neither Malke et al nor Goldstein et al teach a fusion protein comprising streptokinase and either or both of the fibronectin-derived 1/2 or 4/5 fibrin binding domain pairs. Matsuka et al teach the structure of fibrin binding domains 1-5 of fibronectin and that domains 4 and 5 form the critical fibrin-binding site of fibronectin (pg 9544, parg 2; Fig 9). It would have been

obvious to a person of ordinary skill in the art to combine the teachings of Malke et al or Goldstein et al with Matsuka et al to prepare a fusion protein comprising streptokinase and the fibrin binding domains 4 and 5 of fibronectin. Motivation to do so is provided by Dawson et al wherein they teach the following. Fibrinolytic therapy using streptokinase and other plasminogen activators has become widespread (col 1, lines 39-42). A major problem with these agents is that they are not thrombus specific, as they activate plasminogen in the general circulation (col 1, lines 49-52). An approach to enhancing fibrinolysis and inhibition of blood clotting is based on the use of fusion proteins that are activated specifically at the site of blood clotting (col 2, lines 1-5), such as fusion proteins that bind fibrin. Motivation is also provided by Malke et al, who teach that one method of targeting streptokinase activity to the site of blood clotting is to use a fusion protein comprising streptokinase and a plasminogen-derived fibrin binding domain (col 1, lines 27-40). A person of ordinary skill in the art would know that the fibronectin-derived fibrin binding domains 4 and 5 of Matsuka et al would serve the same targeting function as the plasminogen-derived fibrin binding domains of Malke et al and the anti-fibrin antibody of Goldstein et al.

Neither Malke et al, Goldstein et al, Matsuka et al, nor any combination thereof teach a fusion protein comprising streptokinase, the fibronectin-derived fibrin binding domains 4 and 5, with a flexible linker between. However, the use of flexible linkers between components of fusion proteins was well-known in the art. In fact, Dawson et al teach a fusion protein comprising a streptokinase component and a flexible intergenic linker that promotes thrombus-specific activation of streptokinase via clot-specific cleavage of the linker (col 2, parg 1). It would be obvious to a person of ordinary skill in the art to use the flexible linker of Dawson et al

between the streptokinase domain and the fibronectin-derived fibrin binding domains 4 and 5 of the fusion protein rendered obvious by Malke et al or Goldstein et al in view of Matuska et al, as described above. Motivation to do so is provided by Dawson et al, wherein they teach that their flexible linker allows clot-specific activation of streptokinase. The expectation of success is high, as recombinant methods for making fusion proteins are well-known in the art. Thus, based on the problem to be solved, the state of the art, and knowledge of the skilled artisan, Claims 34-37, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and further in view of Dawson et al, 1995.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and further in view of Dawson et al, 1995. Chimeric proteins rendered obvious by the combination of Malke et al, or Goldstein et al in view of Matsuka et al and Dawson et al are described above. Matsuka et al further teach that fibronectin is covalently linked to fibrin via Factor XIII transglutaminase activity (pg 9439, parg 1), while Dawson et al further teach a streptokinase chimeric protein comprising a linker that is a target for Factor XIII transglutaminase (col 2, parg 1). It would be obvious to a person of ordinary skill in the art to include, within the chimeric proteins described above, a linker that is a target for Factor XIII transglutaminase. Motivation to do so derives from the desire to covalently attach the streptokinase component to the fibrin clot in order to stably target the clot for activation of plasminogen. The expectation of success is high, as recombinant methods for making fusion proteins are well-known in the art. Therefore, Claim 38 is rejected

under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and further in view of Dawson et al, 1995.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and Dawson et al, 1995 and further in view of Jackson et al, 1986. Chimeric proteins rendered obvious by the combination of Malke et al or Goldstein et al in view of Matsuka et al and Dawson et al are described above. Said combination fails to teach a streptokinase component comprising residues 1-383 of streptokinase. Jackson et al teach that a polypeptide consisting of residues 1-383 of streptokinase activates plasminogen after a lag (Fig 2). It would be obvious to a person of ordinary skill in the art to modify the chimeric proteins described above to comprise residues 1-383 but not residues 384-414 of streptokinase. Motivation to do so derives from the desire to limit activation of circulating plasminogen and promote the activation of clot-associated plasminogen, upon binding of the chimeric protein to fibrin. The expectation of success is high, as methods for making recombinant proteins are well known in the art. Therefore, Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and Dawson et al, 1995 and further in view of Jackson et al, 1986.

Claims 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994, Dawson et al, 1995, and Jackson et al, 1986 and further in view of Huston et al, 1988. Chimeric proteins rendered obvious by the combination of Malke et al or Goldstein et al in view of Matsuka et al, Dawson et al, and Jackson et al are described above. Said combination does not

teach chimeric proteins having a linker comprising -Gly-Gly-Gly-. However, the use of the peptide -Gly-Gly-Gly- within a linker is well known in the art. For example, Huston et al teach using $(\text{-Gly-Gly-Gly-Gly-Ser})_3$ as a linker (pg 5879, parg 5). It would be obvious to a person of ordinary skill in the art to include, within the chimeric proteins of Claim 42 a $(\text{-Gly-Gly-Gly-Gly-Ser})_3$ linker. Motivation to do so derives from Huston et al, wherein they teach that, "the linker should not exhibit a propensity for ordered secondary structure or any tendency to interfere with domain folding. Thus the 15-residue sequence was selected" (pg 5879, parg 4). The expectation of success is high, as methods for making recombinant proteins comprising linkers are well known in the art. Therefore, Claims 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994, Dawson et al, 1995, and Jackson et al, 1986 and further in view of Huston et al, 1988.

Claims 47, 48, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994, Dawson et al, 1995, and Jackson et al, 1986 and further in view of Larocca et al, 2000 (filing date 29-AUG-1997). The chimeric proteins taught by the combination of Malke et al or Goldstein et al in view of Matsuka et al, Dawson et al, and Jackson et al, 1986 are described above. Said combination does not teach a chimeric protein wherein the fibrin binding domains are at both the N- and C-terminus of streptokinase. However, construction of fusion protein comprising binding domains at both the N- and C-terminus was known in the art. Larocca et al teach a fusion protein comprising an antibody at both the N- and C-terminus (col 21, lines 40-41). It would be obvious to a person of ordinary skill in the art to construct a fusion protein comprising streptokinase

wherein the fibrinogen-derived fibrin binding domains 4 and 5 are linked at both the N- and C-terminus. Motivation to do so is based on the desire to optimize the binding of the chimeric protein to fibrin. The expectation of success is high, as methods for making chimeric proteins are well known in the art. Therefore, Claims 47, 48, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994, of Dawson et al, 1995, and Jackson et al, 1986 and further in view of Larocca et al, 2000.

Claim 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Goldstein et al, 1996 in view of Matsuka et al, 1994 and Dawson et al, 1995 and further in view of Kobayashi et al, 1991. Chimeric proteins rendered obvious by the combination of Malke et al or Goldstein et al in view of Matsuka et al and Dawson et al are described above. Said combination does not teach pharmaceutical compositions comprising the chimeric proteins and either human serum albumin or mannitol. However, it is known in the art that human serum albumin or mannitol can be added to pharmaceutical compositions to stabilize enzymes (Kobayashi et al; col 1, parg 5-6). It would be obvious to a person of ordinary skill in the art to include human serum albumin or mannitol in pharmaceutical compositions comprising the chimeric proteins rendered obvious by the combination of Malke et al or Goldstein et al in view of Matsuka et al and Dawson et al. As stated above, motivation to do so is provided by the desire to stabilize the enzymatic activity. The expectation of success is high, as pharmaceutical compositions comprising enzymes and human serum albumin or mannitol are well known in the art. Therefore, Claim 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993

or Goldstein et al, 1996 in view of Matsuka et al, 1994 and Dawson et al, 1995 and further in view of Kobayashi et al, 1991.

Interview Summary

It is acknowledged that Applicants' representative, Raja Bawa, telephonically contacted Drs. Michael Woodward and Kathleen Kerr on or about February 15, 2006, whereby Applicants requested that the rejection of Claims 34-54 under 35 U.S.C. 103(a), as set forth in the Final Rejection of February 10, 2006, be withdrawn. As conveyed to the Examiner, in one or both of said conversations, Applicants' representative argued that the skilled artisan would not be motivated to combine the teachings of Malke et al, 1993 or Goldstein et al, 1996 with Matsuka et al, 1994 and Dawson et al, 1995 to make Applicants' invention, because the product rendered obvious by said teachings, a fusion protein comprising streptokinase and the fibrinogen-derived fibrin binding domains, has no advantage, i.e., is not better than, the fusion protein comprising streptokinase and the plasminogen-derived fibrin binding domains, as taught by Malke et al, or the fusion protein comprising streptokinase and an anti-fibrin antibody, as taught by Goldstein et al.

Response

This argument is not found to be persuasive for the following reasons.

(A) It is acknowledged that, regarding the rational for supporting a rejection under 35 USC 103(a), MPEP 2144 states: "The expectation of some advantage is the strongest rationale for combining references". However, MPEP 2144 does not state that an advantage is required for motivation to combine (Examiner's emphasis).

(B) Settled law teaches that motivation to combine references for a rejection under 35 USC 103(a) is based on the utility, per se, of the product rendered obvious and does not require that said product provides an advantage over, or is better than, products known in the art. In *In re Fulton*, 391 F.3d 1195, 73 USPQ2d 1141 (Fed. Cir. 2004), the court emphasized that the proper inquiry is "'whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination,' not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." In affirming the Board's obviousness rejection, the court held that the prior art as a whole suggested the desirability of the combination, thus providing a motivation to combine, which need not be supported by a finding that the prior art suggested that the combination claimed by the applicant was the preferred, or most desirable combination over the other alternatives. (MPEP 2143.01)

(C) The Office has asserted that, the fibrinogen-derived fibrin binding domain taught by Matsuka et al is equivalent to the plasminogen-derived fibrin binding domain taught by Malke et al. Making it obvious to a person of ordinary skill in the art to substitute the former for the latter in the streptokinase-comprising fusion protein taught by Malke et al. Regarding making a *Prima Facie* case of equivalence, MPEP 2183 states that if the examiner finds that a prior art element (A) performs the function specified in the claim, (B) is not excluded by any explicit definition provided in the specification for an equivalent, and (C) is an equivalent of the means- (or step-) plus-function limitation, the examiner should provide an explanation and rationale in the Office action as to why the prior art element is an equivalent. It is further stated that factors that will support a conclusion that the prior art element is an equivalent are:

(A) the prior art element performs the identical function specified in the claim in substantially the same way, and produces substantially the same results as the corresponding element disclosed in the specification.

B) a person of ordinary skill in the art would have recognized the interchangeability of the element shown in the prior art for the corresponding element disclosed in the specification.

(C) there are insubstantial differences between the prior art element and the corresponding element disclosed in the specification.

As described in the prior action and above, the fibrinogen-derived fibrin binding domain taught by Matsuka et al can perform the identical function, in substantially the same way, as the plasminogen-derived fibrin binding domain taught by Malke et al, i.e, target a fusion protein to a fibrin clot. Said function, for their respective fibrin binding domains, is taught by both Matsuka et al, (Fig 9) and Malke et al (col 1, lines 27-40) and is also the function recited in the instant invention. A person of ordinary skill in the art would have clearly recognized the interchangeability of the two fibrin binding domain elements, both disclosed in the prior art, with one being the corresponding element disclosed in the specification. Furthermore, the specification fails to exclude, by any explicit definition, the fibrin binding domain of fibronectin as an equivalent for the fibrin binding domain of plasminogen. Similarly, the specification fails to exclude, by any explicit definition, a streptokinase fusion protein comprising the fibrin binding domain of fibronectin as an equivalent for a streptokinase fusion protein comprising the fibrin binding domain of plasminogen. Based on the above analysis, it is concluded that, regarding targeting to a fibrin clot, the fibrin binding domains derived from plasminogen and fibronectin are function equivalents. The same analysis is valid for the equivalence of the fusion protein comprising streptokinase and an anti-fibrin antibody, as taught by Goldstein et al.

(D) Regarding substituting equivalents known for the same purpose, MPEP 2144.06 states that, when it is known in the art that two products have the same function, "This, in our

view, presents strong evidence of obviousness in substituting one for the other". The fact that, as stated the above, the fibrin binding domains derived from plasminogen and fibronectin are function equivalents for the desired activity, provides strong evidence of obviousness in substituting the fibrin binding domains derived from fibrinogen for the fibrin binding domains derived from plasminogen in the streptokinase fusion protein taught by Malke et al. The same analysis is valid for substitution of the anti-fibrin antibody, as taught by Goldstein et al.

(E) As described in (A)-(D), motivation to combine references does not require that the invention rendered obvious have an advantage over the prior art. Nonetheless, the skilled artisan would be further motivated to make the invention of Claims 34-54, as rendered obvious by the combination of Malke et al, 1993 in view of Matsuka et al, 1994 and Dawson et al, 1995, because said invention does have an advantage over the prior art. The fibrinogen-derived fibrin binding domain has an affinity for fibrin of 0.8μM (Williams et al, 1994, Fig 2; Rostagno et al, 1994, pg 31942, parg 2 (IDS)), while the plasminogen-derived fibrin binding domain has an affinity for fibrin of only 51 μM (Lucas et al, 1983, Table 1). Thus, a streptokinase fusion protein comprising the fibrin binding domains of fibronectin would more efficiently target to the fibrin clot than a fusion protein comprising the plasminogen-derived fibrin binding domain. Said advantage would further motivate the skilled artisan to make the invention of Claims 34-54, as rendered obvious by the combination of Malke et al, 1993 in view of Matsuka et al, 1994 and Dawson et al, 1995.

The skilled artisan would also be further motivated to make the invention of Claims 34-54, as rendered obvious by the combination of Goldstein et al, 1996 in view of Matsuka et al, 1994 and Dawson et al, 1995, because said invention does have an advantage over the prior art.

The fibrin binding component of the streptokinase fusion protein taught by Goldstein et al is a Fab fragment of an anti-fibrin antibody, which has a size of 50kD (Fig 2A). In contrast, the fibronectin-derived fibrin binding domain 4 and 5 has a size of 11kD (Matsuka et al; Table 1). Thus, a streptokinase fusion protein comprising the fibrin binding domains of fibronectin would more efficiently diffuse into the fibrin clot than a fusion protein comprising the anti-fibrin antibody. Said advantage would further motivate the skilled artisan to make the invention of Claims 34-54, as rendered obvious by the combination of Goldstein et al, 1996 in view of Matsuka et al, 1994 and Dawson et al, 1995.

For these reasons and those provided in the prior action, rejection of Claims 34-54 under 35 USC 103(a) is maintained.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that Applicants identify support, within the original application, for any amendments to the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Swope, Ph.D.
Art Unit 1656

SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER